REMARKS

This Amendment, filed in reply to the Office Action dated April 15, 2010, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Status of Claims and Amendment

Claims 5, 6 and 27-41 are all the claims pending in the Application. Claims 1-4, 7-26, and 42-46 were previously canceled. Claims 5, 6 and 27-41 are examined on the merits to the extent they read on G-CSF, M-CSF, IL-2, vincristine, cyclophosphamide, etoposide and methotrexate as species of the claimed agent. Claims 5, 6 and 27-41 are rejected.

Claim 5 has been amended to remove "IL-2" without prejudice or disclaimer.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Information Disclosure Statements

Applicants thank the Examiner for returning a signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed December 22, 2009, indicating consideration of the references therein.

Claims 5, 6 and 27-41 are Patentable Under 35 U.S.C. § 103(a)

On page 3 of the Office Action, the Examiner rejects claims 5, 6 and 27-41 under 35 U.S.C. § 103(a) as allegedly being obvious over Shitara *et al.* (U.S. Patent Application Pregrant

Publication No. 2003/0175273) in view of Taub *et al.* (U.S. Patent No. 6,762,174), essentially for the same reasons as set forth in the Office Action mailed July 22, 2009.

The Examiner maintains the position that those of ordinary skill in the art would readily have combined the *unconjugated* anti-CCR4 antibody of Shitara *et al.* with an additional therapeutic agent, such as vincristine, cyclophosphamide, etoposide or methotrexate, with the expectation of producing a chemotherapeutic composition *exhibiting synergy in vivo*. Similarly, the Examiner contends that those of ordinary skill in the art would readily have incorporated a cytokine, such as G-CSF, M-CSF or IL-2, into the antibody composition of Shitara *et al.*, so as to activate immune cells, thereby boosting the patient's immune response against the cancer, citing paragraph [0163] of Shitara *et al.* in support.

In response to Applicants' previous arguments that the claimed invention possesses properties that would have been unexpected to those of ordinary skill in the art at the time of the invention, *i.e.*, synergy in the treatment of CCR4-expressing cancers *in vivo*, the Examiner takes the position that the experimental evidence proffered in support of synergy is insufficient to rebut the rejection; the Examiner makes three main arguments in this regard, depending on the particular species of agent used in combination with the claimed anti-CCR4 antibody.

First, regarding the combination of anti-CCR4 antibody and IL-2, described in Example 1 and Figure 1 of the specification as filed, the Examiner takes the position that because the experiments therein were performed *in vitro*, rather than *in vivo*, the proffered data is not commensurate with claim scope, because Applicants claim a method for treating "a patient," (*i.e.*, an *in vivo* method).

Second, regarding the combination of anti-CCR4 antibody with either vincristine, cyclophosphamide, or methotrexate, the Examiner takes the position that the difference in tumor

size between the negative control and the respective antibody-agent *combination* is "not significantly greater" than the sum of the differences in tumor size when each component (*i.e.*, the antibody and agent) is administered individually. In other words, the Examiner takes the position that these agents, when administered in combination with the anti-CCR4 antibody, produce no more than an *additive* effect; the Examiner postulates that such an additive effect would be expected based on the increase in the total amount of components administered. *See* the paragraph bridging pages 5 and 6 of the outstanding Office Action.

Third, regarding the combination of anti-CCR4 antibody with either etoposide or G-CSF, the Examiner appears to acknowledge that the difference in tumor size between the negative control and the respective antibody-agent combination is greater than the sum of the differences in tumor size from using each component individually, *i.e.*, *a greater than additive effect*. However, the Examiner proceeds to state that "it is not clear [if such] effect is a result of true synergy or due to an increase in the total amount of components administered." *See* page 6, 2nd paragraph, of the outstanding Office Action.

Furthermore, in response to Applicants' arguments that those of ordinary skill in the art would have found the synergistic treatment exhibited by the presently claimed method to be unexpected, in part due to the high degree of unpredictability in the pertinent art as to which combination therapies exhibit synergy, the Examiner attempts to rebut such arguments on the ground that Applicants are merely "arguing limitation[s] not claimed." *See* page 7, 4th paragraph, of the outstanding Office Action. Moreover, in this same section, the Examiner alleges that Taub *et al*. discloses that "anti-cancer agents such as vincristine, cyclophosphamide, etoposide or methotrexate would produce synergism in treating cancer," such that those of

ordinary skill in the art, having read Shitara *et al.* and Taub *et al.*, would have produced Applicants' claimed combination with an expectation that synergy would result.

With regard to the Examiner's first argument, Applicants note the proffered data is commensurate with claim scope inasmuch as those of skill in the art would reasonably extend the probative value of the *in vitro* data to the presently claimed *in vivo* method. In this respect, Applicants' position is supported by relevant law, *In re Kollman*, 595 F.2d 48 (C.C.P.A. 1979)), in which the nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof.

With regard to the Examiner's second argument, namely that the combination of anti-CCR4 antibody with either vincristine, cyclophosphamide, or methotrexate does not exhibit synergy because the reduction in tumor size obtained with such *combinations* vis-à-vis the control sample is allegedly "not significantly greater" than the sum of the reductions in tumor size obtained using the antibody and agent individually, Applicants strongly disagree. In making this argument, the Examiner appears to be focusing on the data in Figures 2, 3 and 5, and appears to require a showing that the claimed combination reduces tumor size by an amount *greater* than the sum of the reductions in tumor size observed when the antibody and agent are used alone. For instance, in Example 1, antibody alone reduced tumor volume (V/V0) by 0.57 (*i.e.*, 57%), and vincristine alone reduced tumor volume (V/V0) by 0.51 (*i.e.*, 51%); the Examiner's position appears to be that, for the combination to exhibit synergy, tumor volume must be reduced by an amount greater than the sum of these two values, *i.e.*, greater than 1.08 (0.51 + 0.57; *i.e.*, greater than 108%). However, the Examiner's position in this regard is flawed, at least because tumor

volume (V/V0) could only be reduced by a maximum of 1 (*i.e.*, a 100% reduction in tumor volume).

In setting forth this standard for synergy, the Examiner appears to improperly construe the Federal Circuit's holding in *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804 (Fed. Cir. 1989)[1] to absolutely require that the reduction in tumor size obtained with the claimed antibody-agent combination be greater than the sum of the actual reduction values observed with each component (*i.e.*, the antibody and agent) individually. However, the Examiner fails to take into account that, in drug therapy combinations where the components in the combination can act simultaneously, and mutually nonexclusively through different mechanisms, the effect of one of the components may reduce the available targets for the second component. That is, if the antibody in the claimed combination has already inhibited a portion of the target cells, then fewer target cells would be available for the agent to inhibit. To account for such in evaluating synergy, one model routinely employed by those of skill in the art to determine the combined effect of the "several effects taken separately," *i.e.*, the combined effect of the anti-CCR4 antibody and the agent, is "Bliss independence" (*i.e.*, "effect multiplication"). In this model, the combined effect of the individual effects is determined by computing the *multiplication product* of the individual effects of the two inhibitors. *See* Fitzgerald *et al.* (*Nature Chem. Biol.*, 2006,

[1] *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804 (Fed. Cir. 1989) (holding that "when an inventor tries to distinguish his [claimed combination] from the prior art by introducing evidence of unexpected "synergistic" properties, the evidence should at least demonstrate "an effect greater than the sum of the several effects taken separately," quoting *Sakraida v. AgPro, Inc.*, 425 U.S. 273, 282 (1976)).

2(9):458-466; attached herewith)[2]. In the present case, Applicants calculated the combined effects of the claimed antibody and agent combinations according to this method (depicted as the "theoretical value" in Tables 1-6), and demonstrated that the actual effect of the claimed combinations is greater than that predicted by effect multiplication. These effects are shown in the Tables of the specification as filed in support of the unexpected synergy of the presently claimed method. The Examiner's attention is respectfully directed to Tables 1-6 in the specification as filed as evidence of the synergistic effects of the claimed invention, *i.e.*, a greater effect than the predicted combined effect, determined according to a routine art-recognized model, namely effect multiplication. As discussed above, and evidenced by Fitzgerald *et al.*, the effect multiplication is a valid model for distinguishing between additive and synergistic effects of therapeutic compositions. Moreover, the court has recognized in *In re Kollman*, 595 F.2d 48, 56 (C.C.P.A. 1979), that effect multiplication is one model useful for determining whether an unobvious synergistic effect exists for a combination of different components.

Furthermore, the synergistic effect provided by the claimed invention would have been unexpected to those of ordinary skill in the art. In this respect, the Examiner appears to assert that that there would have been an expectation of synergy based on Taub *et al.* which discloses that "anti-cancer agents such as vincristine, cyclophosphamide, etoposide or methotrexate would produce synergism in treating cancer," citing column 6, lines 9-26. However, this disclosure in Taub *et al.* has been misconstrued by the Examiner because the statement must be taken in context with the pertinent part of Taub *et al.* stating that "combining compounds of Formula I …

[2] In accordance with M.P.E.P. § 609.05(c), the document cited herein in support of Applicants' remarks is being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

with known anti-cancer agents produces a synergism in treating, preventing, and delaying the clinical appearance of primary cancer or metastatic cancer." Column 6, lines 15-19. That is, Taub *et al.* discloses that it is the presence of compounds of Formula I in combination with other anti-cancer agents that produces synergy. As Applicants previously noted on the record, Taub *et al.* suggests the criticality of including compounds of Formula I in such synergy, and incites no expectation that the recited "known anti-cancer agents" (such as vincristine, cyclophosphamide, etoposide or methotrexate), *in the absence of compounds of Formula I*, would exhibit synergy with other chemotherapeutic agents, much less an antibody.

With regard to the Examiner's third argument, namely that the combination of anti-CCR4 antibody with either etoposide or G-CSF does not exhibit synergy, Applicants note that the Examiner appears confused with this argument. The Examiner contends that while the reduction in tumor size obtained with such *combinations* vis-à-vis the control sample is greater than the sum of the reductions in tumor size obtained using the antibody and agent individually, "it is not clear [if such] effect is [merely] a result of … an increase in the total amount of components administered." However, even assuming *arguendo* that the Examiner's standard for determining synergy were correct, *i.e.*, an effect greater than the sum of the values observed when the antibody and agent are used individually (rather than effect multiplication), the purpose of calculating the sum is to account for the increased dosage when the components are combined. Furthermore, Applicants have submitted herewith, scientific evidence to establish effect multiplication as a valid model for determining synergy between two chemotherapeutic treatments that act on different targets (such as Fitzgerald *et al.*, discussed above). Accordingly, Applicants submit factual evidence establishing the failure of other therapeutic antibodies for the treatment of cancer to exhibit synergy when co-administered with another chemotherapeutic

agent or cytokine. Such evidence support Applicants' position that the pertinent art is unpredictable to the extent that those of ordinary skill in the art would have found Applicants' demonstration of synergy to be unexpected, and nonobvious.

Further, in this regard, while the Examiner attempts to dismiss Applicants' arguments of unpredictability on the basis that Applicants are merely "arguing limitation[s] not claimed," this argument is meritless. Although the Examiner takes the position that Applicants arguments of synergy are unpersuasive, in part, because the claims do not recite use of a "synergistic composition," the Examiner is reminded that unexpected results need not be recited in the claims, but rather, only need to be possessed by the subject matter of the claims.[3]

Withdrawal of the rejection under 35 U.S.C. § 103(a), is respectfully requested.

Obviousness-Type Double Patenting Rejections

On page 9 of the Office Action, the Examiner *provisionally* rejects Claims 5, 6 and 27-46 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 54, 57-70, 74-75 and 81-84 of earlier-filed copending Application No. 11/969,555, in view of Shitara *et al.* (U.S. Patent Application Pregrant Publication No. 2003/0175273) and Taub *et al.* (U.S. Patent No. 6,762,174).

The Examiner has acknowledged Applicants' request to hold this rejection in abeyance until such time as patentable subject matter is identified.

[3] *See, e.g., In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007); and *In re Chu*, 66 F.3d 292, 298-99 (Fed. Cir. 1995).

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: October 14, 2010